Original Contributions

Long-term Protection From Myocardial Ischemic Events in a Randomized Trial of Brief Integrin β_3 Blockade With Percutaneous Coronary Intervention

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Context.—Abciximab, a monoclonal antibody fragment against the platelet receptor $\alpha_{IIb}\beta_3$ integrin, prevents platelet aggregation. A randomized, placebo-controlled study showed that abciximab improves outcomes for patients undergoing percutaneous coronary angioplasty at 30 days and at 6 months.

Objective.—To determine whether abciximab improves outcomes 3 years after coronary angioplasty.

Design.—Double-blind, placebo-controlled, randomized trial.

Setting.—A total of 56 academic and community hospitals in the United States.

Patients.—A total of 2099 high-risk patients undergoing coronary angioplasty were randomized. Sufficient time elapsed for 2.5 years of follow-up among 2001 patients and for 3 years of follow-up among 1599 patients.

Interventions.—Abciximab bolus of 0.25 mg/kg followed by infusion at 10 µg/min for 12 hours; abciximab bolus of 0.25 mg/kg followed by placebo infusion; or placebo bolus followed by placebo infusion.

Main Outcomes Measures.—The primary outcome was the composite of death, myocardial infarction, or coronary revascularization. Secondary outcomes were death, myocardial infarction, or coronary revascularization individually. Subgroups having refractory unstable angina or evolving myocardial infarction and having different elevations of creatine kinase during initial angioplasty were analyzed.

Results.—At 3 years, composite end points occurred in 41.1% of those receiving abciximab bolus plus infusion; 47.4% of those receiving abciximab bolus only; and 47.2% of those receiving placebo only (for abciximab bolus plus infusion vs placebo, P=.009). Death occurred in 6.8%, 8.0%, and 8.6%, respectively (for abciximab bolus plus infusion vs placebo, P=.20); myocardial infarction in 10.7%, 12.2%, and 13.6%, respectively (for abciximab bolus plus infusion vs placebo, P=.08); and revascularization in 34.8%, 38.6%, and 40.1%, respectively (for abciximab bolus plus infusion vs placebo, P=.02). Among those with refractory unstable angina or evolving myocardial infarction, death occurred in 5.1%, 9.2%, and 12.7%, respectively (for abciximab bolus plus infusion vs placebo, P=.01). Death rates increased as periprocedural creatine kinase levels increased.

Conclusions.—Abciximab bolus with infusion given at the time of coronary angioplasty improves outcomes as long as 3 years after the procedure.

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A complete list of the Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication (EPIC) Investigator Group can be found in *Lancet* 1994;343:881-886.

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THE MAJOR LIMITATION of percutaneous coronary intervention is the frequency of coronary renarrowing, resulting in the need for repeat procedures or bypass surgery, or both, in nearly half of patients by 1 year of follow-up.[1-3] To date, the only intervention that has been shown to significantly reduce the rate of recurrence is stenting, which has been

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associated with an approximate 30% reduction of the need for repeat procedures, or 10 per 100 patients treated.[4-6] A large number of pharmacological agents have failed to reduce restenosis or improve long-term clinical outcomes,[7-14] and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abciximab, a monoclonal antibody fragment directed against the β_3 integrin.[15] It was unclear whether this particular benefit would be sustained over long-term follow-up. To determine whether the effects of abciximab would continue beyond 6 months, we maintained the double-blind and performed clinical follow-up 2.5 years after the index percutaneous coronary revascularization procedure.

METHODS

The clinical protocol has previously been described in detail.[15,16] The protocol was approved by each hospital's institutional review board. All patients provided informed consent. Briefly, patients who were considered to be at increased risk of ischemic complications during balloon angioplasty or directional atherectomy because of evolving myo-

Table 1.—Baseline Characteristics of Patients With Complete Long-term Follow-up*

Characteristics	Placebo (n=662)	Bolus (n=683)	Bolus + Infusion (n=678)
Median age, y	61	60	62
Male	484 (73.1)	477 (72.0)	486 (71.7)
Median weight, kg	84	82	82
Risk factors			
Diabetes	168 (25.4)	156 (23.5)	158 (23.3)
Hypertension	362 (54.7)	368 (55.5)	363 (53.5)
Elevated cholesterol	355 (53.6)	368 (55.5)	352 (51.9)
History of smoking	202 (30.5)	232 (35.0)	209 (30.8)
Vascular disease			
Peripheral	55 (8.3)	56 (8.5)	62 (9.1)
Cerebral	20 (3.0)	25 (3.8)	31 (4.6)
Previous infarction			
None	305 (46.1)	275 (41.5)	282 (41.6)
>30 d	160 (24.2)	179 (27.0)	179 (26.4)
8-30 d	83 (12.5)	81 (12.2)	93 (13.7)
<8 d	185 (28.0)	192 (29.0)	192 (28.3)
Previous coronary procedure			
Angioplasty	164 (24.8)	132 (19.9)	149 (22.0)
Bypass surgery	101 (15.3)	94 (14.2)	110 (16.2)
Diseased vessels			
1	358 (54.2)	343 (51.7)	376 (55.5)
2	192 (29.1)	220 (33.2)	211 (31.1)
3	111 (16.8)	100 (15.1)	91 (13.4)
Coronary procedures			
Balloon angioplasty	584 (88.4)	590 (89.3)	593 (87.9)
Atherectomy	29 (4.4)	26 (3.9)	31 (4.6)
Both	35 (5.3)	37 (5.6)	34 (5.0)

*All values are No. (%) except where otherwise indicated.

cardial infarction (MI), unstable angina, or unfavorable demographic or lesion morphologic features were considered eligible. Patients received 325 mg of aspirin per day, with the first dose given at least 2 hours before the procedure. Intravenous heparin sodium was administered during the procedure to achieve an activated clotting time of at least 300 seconds. Patients were randomly assigned to 1 of 3 treatment groups: placebo bolus and placebo 12-hour infusion, 0.25-mg/kg bolus of abciximab (ReoPro, Centocor, Inc, Malvern, Pa) and a placebo infusion, or 0.25-mg/kg bolus of abciximab with an abciximab 12-hour infusion at 10 μg/min. The bolus was administered 10 minutes before performing the actual coronary revascularization.

The primary end point findings of the composite of death from any cause, MI, or urgent coronary revascularization at 30 days or the composite of death, MI, or any coronary revascularization at 6 months, have been previously reported.[15,16] For the long-term follow-up, the same composite end point of death from any cause, MI, or any coronary revascularization procedure was used. The diagnosis of MI during the follow-up period required either a new significant Q wave of 0.04 second or more in duration or with a depth above one quarter of the corresponding R wave amplitude in 2 or more contiguous leads, or a creatine kinase myocardial band greater than twice the upper limit of normal. For the purpose of studying the effects of the size of the periprocedural MI on late survivorship, patients who were alive at 30 days were analyzed as a function of the ratio of peak postprocedural creatine kinase over the upper limit of normal. The high-risk group of patients with refractory unstable angina (having chest discomfort and electrocardiographic changes while receiving medical therapy) and evolving MI (<12 hours from symptom onset) was prospectively defined.[16]

Data were collected by study coordinators on separate long-term follow-up questionnaires. The National Death Index (Public Health Service, Centers for Disease Control and Prevention, National Center for Health Statistics) was searched to verify mortality in patients who died and to determine mortality in patients who were otherwise lost to follow-up. Besides survival status, ascertainment of the events of MI, percutaneous or surgical coronary revascularization, stroke, or need for blood transfusion was obtained. Source documentation for events identified on the questionnaire were collected for blinded review by an independent end point committee. All patients were reviewed and end points adjudicated by this committee. The investigators and the sponsor remained blinded to the treatment assignment of the individual patients.

Median follow-up for mortality was 3.1 years with 99.5% completeness of follow-up at 1 year; 99.1% at 2 years; 97.0% at 2.5 years; and 62.7% at 3 years. Median follow-up for other events was 3.1 years with 96.1% follow-up at 1 year; 95.4% at 2 years; 95.3% at 2.5 years; and 76.2% at 3 years. Follow-up data were obtained in the second half of 1995. Thus, the drop-off after 2.5 years is related to eligibility and not loss of follow-up.

Statistical Analysis

All comparisons reported were by intention to treat. Cumulative event rates were estimated using the Kaplan-Meier method[17] and survival curves were used to display the results graphically. The log-rank test was used to compare event rates between treatment groups. To estimate mean cumulative frequencies of procedures per 100 patients treated, the method of Nelson[18] was used.

Proportional hazards regression models were run for all randomized patients for the 3-year follow-up. The end point used was the composite of death, MI, and repeat revascularization. Treatment group effects were estimated in all models. Models with treatment group and each of the following factors were fit: acute MI or unstable angina vs other high-risk patients, multiple segments treated, graft lesion treated, age greater than or equal to 65 years, female sex, weight, history of diabetes, history of hypertension, history of peripheral vascular disease, history of cerebrovascular disease (stroke or transient ischemic attack), history of MI, history of arrhythmia, history of congestive heart failure, history of hypercholesterolemia, and history of a previous percutaneous transluminal coronary angioplasty. Subsequently, a multivariable model was fit with treatment and all of the above baseline characteristics. Characteristics not associated with outcome at the $P=.05$ level were dropped using a backward stepwise procedure.

RESULTS

The baseline characteristics of the patients who were available for long-term follow-up are presented in Table 1. The cohort of patients with long-term follow-up did not differ in baseline characteristics as compared with the parent group of 2099 patients. The demographics for patients without extended follow-up are provided in Table 2. The flow chart of the patient is shown in Figure 1.

The major outcomes are presented in Table 3. For the composite of death, MI, and the need for coronary revascularization at 1 year, there was a 19% reduction

for the abciximab bolus and infusion as compared with placebo (30.8% vs 38.6%, $P=.002$), with little effect of the bolus only. At 3 years, there was a persistent effect, a 13% reduction (41.1% vs 47.2%, $P=.009$). This is graphically presented in Figure 2, which also shows the lack of effect of the bolus-only group.

For the individual components, there was a significant difference in mortality in the prospectively categorized "highest-risk" subgroup, consisting of patients with evolving MI or unstable angina. As shown in Figure 3, there was a 60% reduction (12.7% vs 5.1%) in mortality at 3 years for this highest-risk group ($P=.01$). The benefit of mortality reduction was confined to this subgroup; the remainder of patients had similar mortality rates in each treatment group (7.2% in placebo and 7.4% in bolus plus infusion, $P=.91$). The relationship between the periprocedural MI and long-term survival is shown in Figure 4. Note how the survival curves diverge over time, especially in patients with more than a 5-fold increase in periprocedural creatine kinase elevation. In Table 4, the risk ratios for death as a function of creatine kinase elevation from index procedure and for the survivorship at 30 days are presented.

The effect on MI during follow-up is shown in Table 3. There was a trend supporting durable protection from MI ($P=.08$), with little change over time in the absolute and relative benefit of the abciximab bolus and infusion compared with placebo. The most frequent adverse outcome in long-term follow-up after percutaneous coronary intervention is the need for revascularization. No late bleeding complications, strokes, or other events were reported or found to be attributable to participation in the trial. There was further benefit beyond 6 months from 8 per 100 patients avoiding repeat procedures to approximately 12 events saved per 100 patients treated with abciximab bolus and infusion compared with placebo. The effect of preventing 12 repeat procedures per 100 patients was a stable benefit throughout the first 2 years of long-term follow-up, and even at 3 years there was a reduction of 9 per 100 patients treated.

In the single covariate models, diabetes (hazard ratio, 1.3; $P=.002$), multiple segments treated (hazard ratio, 1.4; $P<.001$), graft lesion treated (hazard ratio, 1.6; $P<.001$), age greater than or equal to 65 years (hazard ratio, 1.2; $P=.003$), history of angina (hazard ratio, 1.9; $P<.001$), history of peripheral vascular disease (hazard ratio, 1.4; $P<.001$), history of hypertension (hazard ratio, 1.3; $P<.001$), history of congestive heart failure (hazard ratio, 1.3; $P=.02$), history of MI (hazard ratio, 0.8; $P=.005$), history of percutaneous transluminal coronary angioplasty (hazard ratio, 1.2; $P=.02$), history of coronary artery bypass graft (hazard ratio, 1.4; $P<.001$), and history of cigarette smoking (hazard ratio, 0.8; $P=.02$) were associated with differences in rates of events. In multivariable modeling, some covariates significant in single covariate models dropped out while others not significant in single covariate models became significantly associated with events. The covariates in the final model were bolus plus infusion treatment (hazard ratio, 0.8; $P=.02$), weight (hazard ratio of 0.9 for each 20-kg increment in weight,

Table 2.—Baseline Characteristics of Patients Without Complete Long-term Follow-up*

Characteristics	Placebo (n=34)	Bolus (n=32)	Bolus + Infusion (n=30)
Median age, y	55	58	53.5
Male	22 (64.7)	25 (78.1)	20 (66.7)
Median weight, kg	84.5	85	81.5
Risk factors			
Diabetes	12 (35.3)	7 (21.9)	5 (16.7)
Hypertension	16 (47.1)	11 (34.4)	15 (50.0)
Elevated cholesterol	17 (50.0)	17 (53.1)	13 (43.3)
History of smoking	15 (44.1)	20 (62.5)	18 (60.0)
Vascular disease			
Peripheral	4 (11.8)	4 (12.5)	2 (6.7)
Cerebral	3 (8.8)	0 (0.0)	0 (0.0)
Previous infarction			
None	13 (38.2)	5 (15.6)	6 (20.0)
>30 d	9 (26.5)	14 (43.8)	8 (26.7)
8-30 d	6 (17.7)	10 (31.3)	6 (20.0)
<8 d	11 (32.4)	12 (37.5)	14 (46.7)
Previous coronary procedure			
Angioplasty	6 (17.7)	5 (15.6)	4 (13.3)
Bypass surgery	3 (8.8)	1 (3.1)	3 (10.0)
Diseased vessels			
1	22 (64.2)	17 (53.1)	18 (60.0)
2	9 (26.5)	13 (40.6)	10 (33.3)
3	3 (8.8)	2 (6.3)	0 (0.0)
Coronary procedures			
Balloon angioplasty	31 (91.2)	29 (90.6)	26 (86.7)
Atherectomy	2 (5.9)	1 (3.1)	1 (3.3)
Both	0 (0.0)	2 (6.3)	1 (3.3)

*All values are No. (%) except where otherwise indicated.

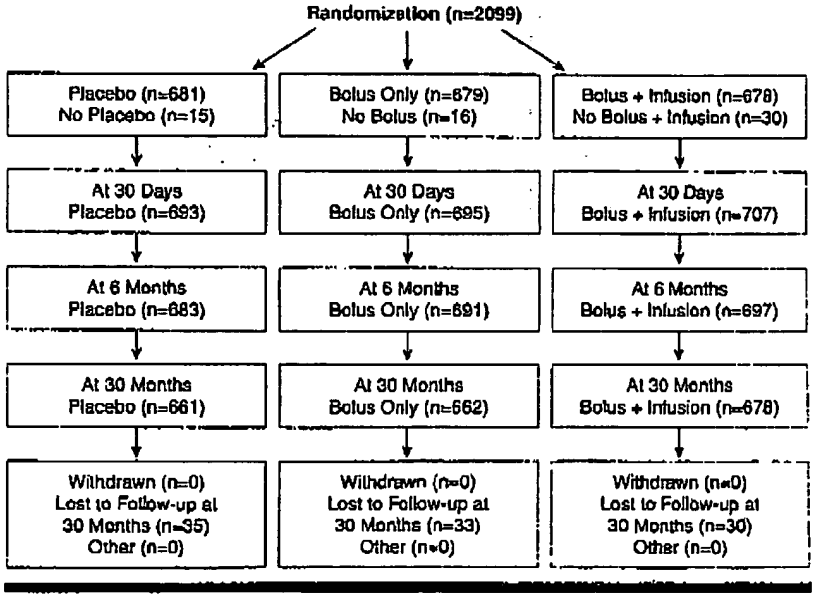
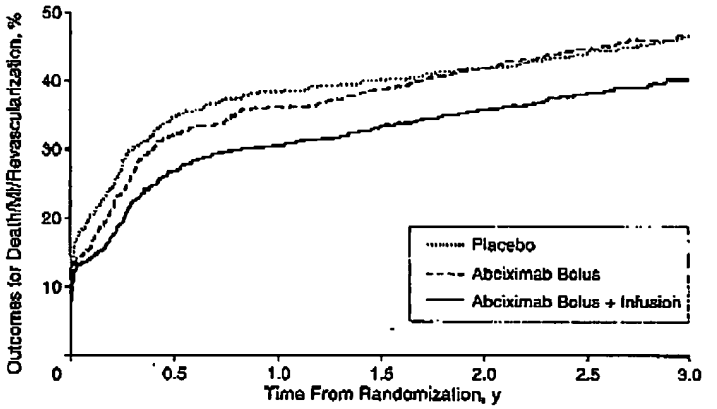


Figure 1.—EPIC Trial flow chart of patients by treatment assignment at 2.5-year follow-up.

Table 3.—Clinical Outcomes: Death/Myocardial Infarction/Any Coronary Revascularization*

End Point	Placebo (n=696)	Bolus (n=698)	Bolus + Infusion (n=709)	P Value	Odds Ratio (95% Confidence Interval)
Composite					
1 year	266 (38.6)	251 (36.3)	216 (30.8)	.002	0.75 (0.63-0.90)
2 years	290 (42.3)	290 (42.4)	253 (36.3)	.009	0.80 (0.68-0.95)
3 years	319 (47.2)	321 (47.4)	283 (41.1)	.009	0.81 (0.69-0.95)
Death					
1 year	31 (4.5)	29 (4.2)	30 (4.2)	.841	0.95 (0.58-1.57)
2 years	46 (6.6)	40 (5.8)	37 (5.2)	.277	0.79 (0.51-1.22)
3 years	59 (8.5)	54 (8.0)	47 (6.8)	.202	0.78 (0.53-1.14)
Myocardial infarction					
1 year	77 (11.2)	62 (9.0)	55 (7.9)	.032	0.69 (0.49-0.97)
2 years	84 (12.4)	73 (10.6)	64 (9.3)	.057	0.73 (0.53-1.01)
3 years	91 (13.6)	81 (12.2)	72 (10.7)	.075	0.76 (0.56-1.03)
Revascularization					
1 year	221 (32.6)	207 (30.4)	178 (25.6)	.004	0.75 (0.62-0.91)
2 years	242 (36.0)	237 (35.3)	207 (30.2)	.013	0.79 (0.66-0.95)
3 years	265 (40.1)	256 (38.6)	234 (34.8)	.021	0.81 (0.68-0.97)

*P value and odds ratio represent the comparison of bolus + infusion vs placebo. All values are No. (%) except where otherwise indicated.



Completed Follow-up							
Placebo	696	683	669	664	662	661	528
Bolus	695	691	665	663	663	652	540
Bolus + Infusion	708	697	683	678	678	678	531

Figure 2.—Composite outcome of death, myocardial infarction (MI), and need for revascularization. At 3 years, P=.009 for risk reduction, abciximab bolus + infusion vs placebo.

P=.04), history of diabetes (hazard ratio, 1.2; P=.04), multiple segments treated (hazard ratio, 1.4; P<.001), graft lesion treated (hazard ratio, 1.4; P=.006), female sex (hazard ratio, 0.8; P=.04), history of angina (hazard ratio, 1.8; P<.001), history of peripheral vascular disease (hazard ratio, 1.3; P=.03), history of hypertension (hazard ratio, 1.3; P<.001), and history of MI (hazard ratio, 0.9; P=.047). The interpretation of this multivariable model may be problematic because of the variable selection procedure and the possible lack of fit of the proportional hazards model.

COMMENT

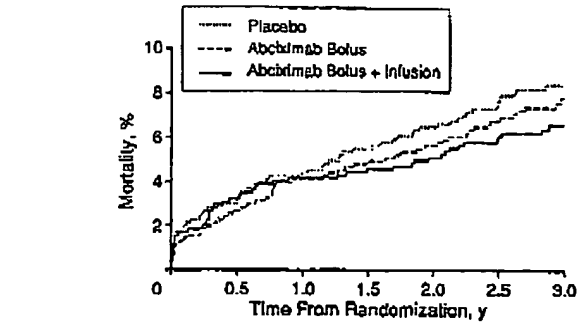
In this extended follow-up of the first large cohort of patients to receive abciximab therapy, the findings of protection from death, MI, and repeat revascularization procedures after percutaneous coronary intervention are important. The antibody fragment had a consistent, positive effect on each component of the 3 outcome composite events. Until now, no pharmacological therapy had demonstrated improved clinical outcomes after coronary intervention, and while the 6-month data with abciximab were encouraging,[15] further observation was required to determine whether the salutary effect would be durable.

The sustained benefit at 2.5 years of follow-up was unexpected, given the expectation that new coronary atherosclerotic events might arise from different lesions or coronary arteries by 1 year after the index percutaneous coronary revascularization procedure. Previous studies using intravascular ultrasound and angiography have shown that once a focal atherosclerotic coronary lesion develops, there is extensive disease throughout the coronary tree.[19] With the brief (12-hour) treatment directed at platelet aggregation, durable effects on major ischemic complications seemed unlikely. Thus, it was anticipated that after 1 year there might be convergence of the event curves owing to the natural history of coronary artery disease.

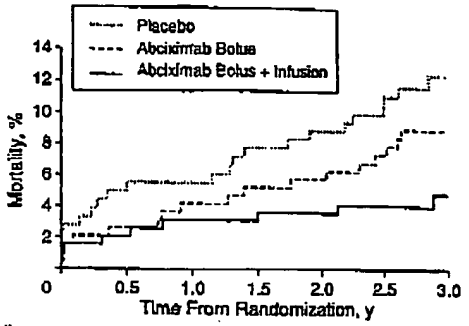
Moreover, the reduction in mortality in patients who initially had acute coronary syndromes was striking and only became substantial subsequent to the first year of follow-up. Importantly, several observational studies have now reported an association between elevated periprocedural creatine kinase and late (beyond 1 year) survival.[20-25] But until now, no trial had demonstrated that an intervention that reduced the incidence of periprocedural MI would result in improved survival. This considerably strengthens the potential linkage and cause-and-effect relationship between periprocedural MI and late cardiac death.

The explanation of the sustained benefit may stem from the dual action of the abciximab antibody Fab fragment. Although the antibody was developed to bind to the IIb/IIIa ($\alpha_{IIb}\beta_3$) integrin,[26] there is full cross-reactivity with the $\alpha_v\beta_3$ integrin (vitronectin receptor). The $\alpha_v\beta_3$ integrin is highly expressed on the surface of activated endothelial cells and smooth muscle cells.[27] Smooth muscle cell migration is strongly inhibited by $\alpha_v\beta_3$ integrin blockade. This has been found in smooth muscle cell culture with insulin growth factors[28] and in vivo after balloon injury in experimental models.[29,30] The $\alpha_v\beta_3$ receptor is pivotal in modulating the *p53* gene and smooth muscle cell apoptosis,[31] and recent studies in human restenosis have highlighted the potential importance of modulating the *p53* gene.[32,33] Furthermore, the inhibition of both IIb/IIIa and the $\alpha_v\beta_3$ simultaneously has an important effect on inhibiting thrombin generation[34] beyond that which is achieved with inhibiting either of these integrins separately.

Until more studies are completed with extended follow-up, one important question is the application of abciximab therapy for patients undergoing percutaneous coronary intervention. With the preparation approved by the Food and Drug Administration since 1995 for coronary intervention, the findings of this study provide evidence of further durability of the benefit over time. Another large-scale trial of abciximab in patients undergoing routine, not high-risk coronary intervention, with use of lower conjunctive doses of heparin than previous



Completed Follow-up							
Placebo	696	696	694	692	691	677	440
Bolus	695	695	691	691	688	669	436
Bolus + Infusion	708	706	704	703	701	689	439



Completed Follow-up							
Placebo	179	179	179	178	178	170	101
Bolus	168	168	168	168	167	160	98
Bolus + Infusion	188	188	186	187	187	180	99

Figure 3.—Mortality event curves for overall trial cohort by treatment assignment (left) and mortality for a subgroup of patients with evolving (less than 12 hours) myocardial infarction or unstable angina (right). Reduction in mortality for abciximab bolus + infusion vs placebo had $P=.20$ for entire cohort, but $P=.01$ for the highest-risk subgroup with evolving myocardial infarction or unstable angina.

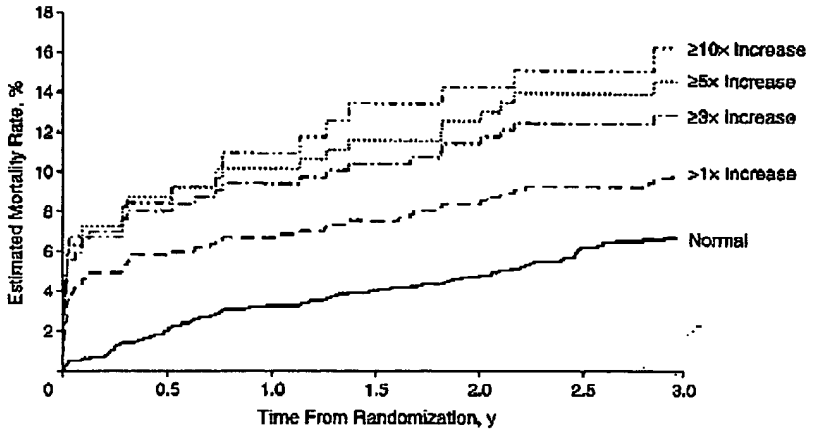


Figure 4.—Mortality for patients with 1-fold to 10-fold increases in periprocedural creatine kinase elevation as compared with patients without creatine kinase elevation. The number of patients and P values for comparisons are ≥1×, n=562, $P=.02$; ≥3×, n=265, $P<.001$; ≥5×, n=205, $P<.001$; ≥10×, n=118, $P<.001$.

Table 4.—Relationship of Periprocedural Myocardial Infarction to Survival

Ratio of Peak Creatine Kinase Elevation Above Normal	Risk Ratios for Death (95% Confidence Interval)	
	From Index Procedure	From 30 Days, Survivors Only
≥1×	1.47 (1.07-2.01)	0.95 (0.65-1.38)
≥2×	1.65 (1.17-2.32)	0.99 (0.64-1.54)
≥3×	1.94 (1.38-2.78)	1.24 (0.79-1.96)
≥5×	2.16 (1.47-3.19)	1.46 (0.89-2.40)
≥10×	2.40 (1.51-3.83)	1.74 (0.96-3.14)

studies, showed that the use of abciximab reduced the incidence of death and MI at 30 days by 58%, without any evidence of an excess of bleeding complications.[35] The use of abciximab in a much larger proportion of patients undergoing coronary intervention requires confirmation of extended benefit in that trial and revised cost-benefit analysis given the price of abciximab of approximately $1350 per patient dose along with current findings of the amplification of benefit with respect to extent, durability, and breadth of the clinical population. More far-reaching, the present study is the first to show prolonged protective effects of an adhesion molecule antagonist in the setting of atherosclerotic coronary disease, a disease with a natural history until now that has been only favorably modulated by aspirin, angiotensin-converting enzyme inhibitors, β-adrenergic antagonists, and hepatic hydroxymethylglutaryl coenzyme A reductase inhibitors.[30-33] This raises the potential of a new biological pathway to exploit for the purpose of stabilizing coronary atherosclerotic disease.

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